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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/012673 A3

(54) Title: METHODS AND REAGENTS RELATING TO INFLAMMATION AND APOPTOSIS

(57) Abstract: The present invention relates to, among other embodiments, protein complexes which include tumor necrosis factor alpha (TNF- $\alpha$ ) and/or tumor necrosis factor alpha receptor (TNFR). Preferably, the complexes comprise at least one polypeptide selected from the group consisting of: NF- $\kappa$ B activating kinase (NAK), RasGAP3, TRCP1, and TRCP2. The present invention further provides assays of identifying a compound for modulating the stability and activity of the complex. Also provided are methods of modulating apoptosis and inflammation, as well as treating TNF- $\alpha$  related diseases.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US03/24340

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 39/395, 38/00; C07K 16/18, 14/00, 14/35; C12N 5/10, 15/63  
 US CL : 424/130.1; 435/7.1, 69.1, 320.1, 325; 514/2; 530/350, 300, 387.1

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1; 435/7.1, 69.1, 320.1, 325; 514/2; 530/350, 300, 387.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
 NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,294,348 B1 (GOEDDEL et al.) 25 September 2001, see entire document.	1-3, 7-9, 11-18, 22-49
Y	MAK et al. Signaling for Survival and Apoptosis in the Immune System. Arthritis Research. 09 May 2002, Vol. 4(Suppl. 3), pages S243-S252 (online version pages 1-19), see entire document.	1-3, 7-9, 11-18, 22-49

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

18 March 2004 (18.03.2004)

Date of mailing of the international search report

27 MAY 2004

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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US03/24340

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claim Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claim Nos.: 4-6,10,19-21 and 50-57 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claims 4-6, 10, 19-21 could not be searched because the CRF was defective and therefore the sequences encoding said molecules could not be searched.
  
3.  Claim Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**  

The additional search fees were accompanied by the applicant's protest.  
No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

PCT/US03/00000

**Continuation of B. FIELDS SEARCHED Item 3:**

WEST 2.1, MEDICINE/BIOTECH (compendium databases on DIALOG) search terms: inventor names, tnf?, tnfr?, tnf receptor?, NAK, TBK1, T2K, TANK, TRAF2? TRADD, TRAP2, NFKB, NF KB, complex?, tumor necrosis factor